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(19)

(54) AMINO OXAZOLE DERIVATIVES

(71) We, LILLY INDUSTRIES LIMITED, a British company of Henrietta House, Henrietta Place, London, W.1., do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:

This invention relates to a class of novel dialkylamino oxagole derivatives which possess activity in the treatment of allergic conditions, to methods of making the novel oxazoles of the invention, to pharmaceutical formulations containing the active compounds of the invention and to methods of treating animals with the active compounds of the invention.

A number of dialkylamino oxazoles, particularly 4-phenyl derivatives see for example *Chemische Berichte*, 1928 (1959) and *Journal of Medicinal Chemistry 11*, 1092, (1967), have been previously described. However, there has been no disclosure or even suggestion that dialkylamino oxazoles might possess utility in treatment of allergic conditions.

Accordingly, in one aspect of the invention there is provided a novel oxazole amine of formula (I):

$$Ar\text{-}NR^1R^2 \qquad (I)$$

wherein Ar represents an optionally substituted oxazolyl group, the amino group $-NR^1R^2$ being attached at the 2-position thereof, and wherein R^1 and R^2 are the same or different and are C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} alkynyl, C_{2-6} alkoxyalkyl, C_{2-6} carboxyalkyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-6} alkyl, optionally substituted phenyl, optionally substituted phenyl-C_{1-6} alkyl or optionally substituted phenyl-C_{2-6} alkenyl; or R^1 and R^2 taken together with the adjacent nitrogen atom form a hetero-cyclic ring containing from 5 to 7 ring atoms;

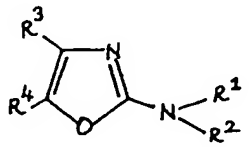
provided that:

(a) that 4-position of the oxazole nucleus cannot be substituted by phenyl, and

(b) when the 4- and 5-position of the oxazole nucleus are both substituted by methyl, R^1 and R^2 cannot both be ethyl.

The oxazole nucleus may be substituted in the 4- or 5-position by a group selected from formyl, carboxyl, hydroxy, C_{1-4} hydroxyalkyl, C_{1-4} alkyl, C_{3-10} cycloalkyl and C_{3-6} acyloxyalkyl and, additionally, in the 5-position by optionally substituted phenyl.

A particularly preferred class of amines of the present invention are those of formula:



(II)

wherein R^1 and R^2 are as defined above and wherein R^3 and R^4 are independently hydrogen C_{1-4} alkyl, C_{1-4} hydroxyalkyl C_{3-10} cycloalkyl or C_{3-6} acyloxyalkyl.

The term "C_{1-6} alkyl" as used herein means a straight or branched chain alkyl group containing from 1 to 6 carbon atoms such as methyl, ethyl, *iso*propyl, *n*-butyl, *s*-butyl, *iso*butyl, *t*-butyl, *n*-amyl, *s*-amyl, *n*-hexyl, 2-ethylbutyl or 4-methylamyl.

Similarly the term "C_{1-4} alkyl" as used herein means a straight or branched chain alkyl group containing from 1 to 4 carbon atoms, namely methyl, ethyl, *iso*propyl, *n*-propyl, *n*-butyl, *iso*butyl, *s*-butyl, *t*-butyl. "C_{1-4} hydroxyalkyl" and "C_{3-6} acyloxyalkyl" mean the aforementioned C_{1-4} alkyl groups substituted with an hydroxy group and acyloxy group respectively. "C_{2-6} alkoxyalkyl" and "C_{1-6} haloalkyl" mean the aforementioned C_{1-6} alkyl groups substituted with an alkoxy group or one or more halogen atoms, such as methoxyethyl, ethoxyethyl, ethoxybutyl, dibromomethyl, trifluoromethyl, 1-chloroethyl, 1,1-dichloroethyl, 1-iodobutyl or pentafluoroethyl.

"C_{3-10} cycloalkyl" means a saturated ring having from 3 to 10 carbon atoms in the ring such as cyclopropyl, cyclobutyl, cyclopentyl, cyclooctyl, or adamantyl.

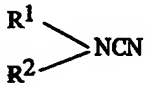
The term "optionally substituted phenyl" as used herein means a phenyl group unsubstituted or substituted by one or more groups which do not substantially alter the pharmacological activity of the compounds of formula I, such as halogen, trifluoromethyl, methyl, methoxy, or nitro groups.

The term "C_{3-6} carboxyalkyl" as used herein means a C_{1-5} alkyl group substituted by a carboxylic acid group. Examples of such groups are carboxymethyl, carboxyethyl, carboxypropyl and carboxybutyl.

Preferred compounds falling within the scope of the amines defined in formula (I) or (II) above are those wherein R^1 and R^2 are C_{1-6} alkyl, C_{3-6} alkynyl, C_{2-6} alkoxyalkyl, C_{3-6} carboxyalkyl, C_{3-6} cycloalkylmethyl, or optionally substituted benzyl, or R^1 and R^2 taken together with the adjacent nitrogen atom form a heterocyclic ring having from 5 to 7 ring atoms, said nitrogen atoms, and optionally an oxygen atom, being the sole heteroatoms.

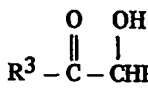
The most preferred oxazole amine compounds in accordance with the invention are those wherein R^1 and R^2 are C_{3-6} alkyl, C_{3-6} alkynyl or optionally substituted benzyl, or R^1 and R^2 taken together with the adjacent nitrogen atom form a heterocyclic ring containing 6 ring atoms of which the sole heteroatoms are the nitrogen atom and, optionally, a single oxygen atom.

According to one aspect of the present invention there is provided a method of preparing an amine of formula (I) or (II) by the reaction of a cyanamide of formula (III):



(III)

wherein R^1 and R^2 are as defined above with a hydroxyketone of formula (IV):



(IV)

wherein R^3 and R^4 are as defined above, to yield the desired tertiary amine directly. This cyclisation reaction may be carried out using an aqueous solvent and an optional co-solvent such as tetrahydrofuran. A suitable catalyst for the reaction is aqueous hydrochloric acid. Alternatively this reaction may be carried out in an inert solvent such as benzene or toluene containing a suitable acid catalyst such as methanesulphonic acid and the water formed by the reaction removed by azeotropic distillation.

Alternatively, the tertiary amines of formula (I) or (II) may be derived from the corresponding secondary amines of formula (V):

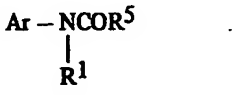
$Ar\text{-}NHR^2$ (V)

wherein Ar and R^2 are as defined above, by alkylation.

The alkylation may be effected by dissolving the amine in a suitable inert, anhydrous, polar solvent such as dimethylformamide, forming an alkali metal salt thereof with an alkali metal hydride, preferably sodium hydride, and then treating the salt with an alkylating agent of formula R^1X where X is a reactive atom such as a halogen atom, for instance, iodine or a reactive group such as an alkyl sulphate group. Alternatively, the abovementioned hydride can be replaced by an appropriate anhydrous alkali metal carbonate such as potassium or sodium carbonate in an inert solvent such as methyl ethyl ketone or dimethyl-

formamide. In the latter case, the reaction mixture is preferably heated to accomplish the alkylation. Of course, alkylating agents and alkylating reaction conditions other than those specified above can be utilised

A further convenient method of preparing certain of the amines of the invention involves the reduction of the corresponding amide of formula (VI):

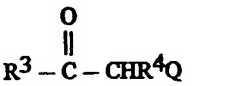


(VI)

wherein Ar and R^1 are as defined above and wherein R^5 and R^2 less a methylene ($-CH_2-$) group, this being derived from reduction of the carbonyl function in the amide. The reduction can be accomplished using a suitable reducing agent such as lithium aluminium hydride. Any suitable inert solvent may be used although the use of tetrahydrofuran is preferred.

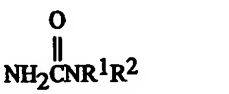
Preparation of the amides of formula (VI) is described in United Kingdom Patent Specification No. 1,497,536.

Compounds of formula (I) or (II) may also be derived from the reaction of a ketahalo derivative of formula (VII):



(VII)

where Q is chlorine or preferably bromine, R^3 is substituted phenyl and R^4 is optionally substituted phenyl, with a substituted urea of formula (VIII):



(VIII)

The reaction may be effected by boiling both reactants together in water.

A further method of preparing compounds of formula (I) or (II) involves reaction of an oxazole derivative of formula (IX):

Ar L (IX)

wherein Ar is as hereinbefore defined and L is chlorine, bromine, iodine or a group of formula -SR, -SOR, or $-SO_2R$ where R is C_{1-8} alkyl, C_{3-8} cycloalkyl, benzyl or phenyl, at the 2-position of the oxazole nucleus, with an amine of formula HNR^1R^2 wherein R^1 and R^2 are as hereinbefore defined, optionally in a solvent such as dioxan.

The preparation of compounds of formula (IX) is illustrated in our copending application No. 24552/75. (Serial No. 1552125).

Compounds of formula (I) and (II) have been shown to be useful in the prophylactic and therapeutic treatment of immediate hypersensitivity diseases including asthma and in the alleviation of *status asthmaticus*. The compounds have low toxicity.

The compounds or compositions of the present invention may be administered by various routes and for this purpose may be formulated in a variety of forms. Thus the compounds or compositions may be adminisered by the oral and rectal routes, topically, parenterally, e.g. by injection and by continuous or discontinuous intra-arterial infusion, in the form of, for example, tablets, lozenges, sub-lingual tablets, sachets, cachets, elixirs, suspensions, aerosols, ointments for example, containing from 1 to 10% by weight of the active compound in a suitable base, soft and hard gelatin capsules, suppositories, injection solutions and suspensions in physiologically acceptable media, and sterile packaged powders adsorbed onto a support material for making injection solutions. Advantageously for this purpose, compositions may be provided in dosage unit form, preferably each dosage unit containing from 5 to 500 mg. (from 5.0 to 50 mg. in the case of parenteral administration, from 5.0 to 50 mg. in the case of inhalation and from 25 to 500 mg. in the case of oral or rectal administration) of a compound of formula (I). Dosages of from 0.5 to 300 mg/kg per day, preferably 0.5 to 20 mg/kg of active ingredient may be administered although it will, of course, readily be understood that the amount of the compound or compounds of formula I or II actually to be administered will be determined by a physician, in the light of all the relevant circumstances including the condition to be treated, the choice of compound to be administered and the choice of route of administration and therefore the above preferred

dosage range is not intended to limit the scope of the present invention in any way.

In this specification, the expression "dosage unit form" is used as meaning a physically discrete unit containing an individual quantitiy of the active ingredient, generally in admixture with a pharmaceutical diluent therefor, or otherwise in association with a pharmaceutical carrier, the quantity of the active ingredient being such that one or more units are normally required for a single therapeutic administration or that, in the case of severable units such as scored tablets, at least one fraction such as a half or a quarter of a severable unit is required for a single therapeutic administration.

The formulations of the present invention normally will consist of at least one compound of formula I mixed with a carrier, or diluted by a carrier, or enclosed or encapsulated by an ingestible carrier in the form of a capsule, sachet, cachet, paper or other container or by a disposable container such as an ampoule. A carrier or diluent may be a solid, semi-solid or liquid material, which serves as a vehicle, excipient or medium for the active therapeutic substance.

Some examples of the diluents or carriers which may be employed in the pharmaceutical compositions of the present invention are lactose, dextrose, sucrose, sorbital, mannitol, propylene glycol, liquid paraffin, white soft paraffin, kaolin, fumed silicon dioxide, microcrystalline cellulose, calcium silicate, silica, polyvinylpyrrolidine, cetostearyl alcohol, starch, modified starches, gum acacia, calcium phosphate, cocoa butter, ethoxylated esters, oil of theobroma, arachis oil, alginates, tragacanth, gelatin, syrup B.P., methyl cellulose, polyoxyethylene sorbitan monolaurate, ethyl lactate, methyl and propyl hydroxybenzoate, sorbitan trioleate, sorbitan sesquioleate and oleyl alcohol and propellants such as trichloromonofluoromethane, dichlorodifluoromethane and dichlorotetrafluoroethane. In the case of tablets, a lubricant may be incorporated to prevent sticking and binding of the powdered ingredients in the dies and on the punch of the tabletting machine. For such purposes there may be employed for instance aluminium, magnesium or calcium stearates, talc or mineral oil.

The following Examples will serve to further illustrate the invention.

EXAMPLE 1

2-(N-Butyl-N-isobutyl)amino-4-methyloxazole

2-Butylamino-4-methyloxazole (7 g, 0.0455 m) in dry DMF (25 cc.) was cooled to 0°C and NaH (2.5 g of a 50% suspension, 0.052 m) was added slowly. After 30 minutes *iso*butyl iodide (8.5 g, 0.046 m) was added dropwise and then the reaction was allowed to stand at room temperature for 11 hours. A red colour developed which disappeared on adding water. Work-up in the normal way gave a pale yellow oil, which was passed through a column of alumina (I, 100 g) which benzene to remove a trace of secondary amine.

The colourless product distilled at 60–61°C/0.1 mm. 4.8 g.

Spectral data, including NMR and infra-red spectra, fully supported the expected structure.

EXAMPLES 2 AND 3

Using the procedure described in Example 1, with appropriate modifications there were similarly prepared:

Ethyl-N-(4-methyl-oxadol-2-yl)-butylamino-acetate b.p. 78°C/0.01 mm 2-(N-Ethoxyethyl-N-butyl)-amino-4-methyloxazole b.p. 76°C/0.01 mm.

EXAMPLE 4

4-Methyl-2-(1-piperidino)-oxazole

5*N*-Hydrochloric acid (10 ml. 0.05 mole equivalents) was added to a solution of N-cyanopiperidine (5.5g. 0.05 mole) in 58% aqueous hydroxyacetone (13 ml. 0.1 mole) and the mixture was stirred at room temperature for 24 hours. The mixture was made alkaline by addition of 2 *N*-aqueous sodium hydroxide (30 ml. 0.06 mole equivalents) diluted with water (150 ml) and extracted with ether (100 ml portions). The combined ether extracts were dried ($MgSO_4$) and evaporated to give the crude title product, which on distillation gave the pure title product (3.1 g. b.p. 74°C/0.1 mm).

EXAMPLES 5 TO 7

By similar procedures to that described in Example 4 there were also prepared:

2-(N-Cyclohexylmethyl-N-ethyl)-amino-4-methyloxazole b.p. 57-58°C/0.01 mm

2-Di-*iso*propylamino-4-methyloxazole b.p. 85° C/13 mm

2-Dibutylmaino-oxazole-4-methanol b.p. 110°/0.07 mm

EXAMPLE 8

2-Di-isopropylamino-4,5-dimethyloxazole

A solution of di-*iso*propylcyanamide (4.3 g., 0.035 mole) acetoin (3.0 g, 0.034 mole) and methanesulphonic acid (2.2 ml, 0.034 mole) in dry benzene was heated under reflux for 2 hours. The water formed during the reaction (0.65 ml, 0.035 mole) was removed by a Dean-Stark trap. The cooled reaction mixture was washed with excess dilute base and with water, was dried ($MgSO_4$) and evaporated to give the crude title product (6.0 g) containing a trace of di-*iso*propylcyanamide. The crude product was purified chromatographically using alumina (200g), eluting with ether, yielding a single-component oil which on distillation under reduced pressure gave the pure title product (4.0 g. b.p. 91°C/11m).

EXAMPLES 9 TO 12

There were also prepared by the method of Example 8 with appropriate modifications:

2-Dibutylamino-4,5-dimethyloxazole b.p. 55–57°C/0.015 mm

4,5-Dimethyl-2-(N-3-methylbut-1-yl-N-propyl)amino oxazole b.p. 66–67°C/0.02 mm

2-(N-ethyl-N-benzylamino)-4-methyloxazole b.p. 106–108°C/0.05 mm

4-methyl-2-(N-methyl-N-butylamino)-oxazole b.p. 105°C/11 mm

EXAMPLE 13

4,5-Dimethyl-2-(4-morpholino)-oxazole

A solution of 2-chloro-4,5-dimethyloxazole (1.4 g. 0.011 mole) in morpholine (2.8 g. 0.032 mole) was heated under reflux for 2 hours. The reaction mixture was then cooled, diluted with water (100 ml) made alkaline with 2 *N* aqueous NaOH (5.4 ml, 0.11 mole equivalents) and twice extracted with ether (50 ml portions). The combined ether extracts were dried ($MgSO_4$) and evaporated to give the crude title product, which on distillation under reduced pressure yielded the pure title product (1.8 g. b.p. 76–77°C/0.015 mm).

EXAMPLE 14

2-(N-Butyl-N-isobutyl)-amino-4-methuloxazole

2-(N-butyl-*iso*butyramido)-4-methyloxazole (5.6 g, 0.025 mole) in dry tetrahydrofuran (25 ml) was added dropwise to a suspension of lithium aluminium hydride in dry tetrahydrofuran (25 ml). The mixture was heated under reflux for 5½ hours. Work-up of the reaction mixture in the normal way gave the title product as a colourless oil (b.p. 60–61°C/0.1 mm) which was indistinguishable from the product of Example 1.

EXAMPLE 15

2-Dibutylamino-4,5-bis-(4 methoxyphenyl)-oxazole

Bis-4-methoxy-desyl-chlorode (11.6 g. 0.04 mole) and N,N-dibutylurea (34.4 g. 0.2 mole) in dry dimethylformamide (50 ml) were heated and stirred at 100°C for 24 hours. The dimethylformamide was removed under reduced pressure and the residue was partitioned between excess dilute aqueous sodium hydroxide and ether. The organic layer was washed twice with water (100 ml portions), dried ($MgSO_4$) and concentrated to give the crude title product. The crude title product was recrystallised from ethanol to yield the pure title product (4.9 g, m.p. 109–111°C).

The products of the examples were characterised by T.L.C. mass spectrometry and NMR data. in all cases the analytical data were in full accord with the expected structures.

WHAT WE CLAIM IS:–

1. An oxazole amine of formula (I):

$$Ar\text{-}NR^1R^2 \quad (I)$$

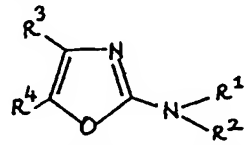
wherein Ar represents an optionally substituted oxazoyl group, the amino group $-NR^1R^2$ being attached at the 2-position thereof, and wherein R^1 and R^2 are the same or different and are C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} alkynyl, C_{2-6} alkoxyalkyl, C_{2-6} carboxyalkyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-6} alkyl, optionally substituted phenyl, optionally substituted phenyl-C_{1-6} alkyl or optionally substituted phenyl-C_{2-6} alkenyl; or R^1

and R^2 taken together with the adjacent nitrogen atom form a heterocyclic ring containing from 5 to 7 ring atoms;

provided that:

(a) the 4-position of the oxazole nucleus cannot be substituted by phenyl, and
(b) when the 4- and 5-positions of the oxazole nucleus are both substituted by methyl, R^1 and R^2 cannot both be ethyl.

2. An oxazole amine as claimed in Claim 1 having the structural formula (II):



wherein R^3 and R^4 are independently hydrogen. C_{1-4} alkyl, C_{1-4} hydroxyalkyl C_{3-10} cycloalkyl or C_{3-6} acyloxyalkyl.

3. An oxazole amine according to Claim 1 to 2 wherein R^1 and R^2 are C_{1-6} alkyl, C_{3-6} alkynyl, C_{2-6} alkoxyalkyl, C_{2-6} carboxyalkyl, C_{3-6} cycloalkyl-methyl, or optionally substituted benzyl, or R^1 and R^2 taken together with the adjacent nitrogen atom form a heterocyclic ring having from 5 to 7 ring atoms, said nitrogen atom, and optionally an oxygen atom being the sole heteroatoms.

4. An oxazole amine according to Claim 1, 2 or 3, wherein R^1 and R^2 are C_{3-6} alkyl, C_{3-6} alkynyl or optionally substituted benzyl, or R^1 and R^2 taken together with the adjacent nitrogen atom form a heterocyclic ring containing 6 ring atoms of which the sole heteroatoms are the nitrogen atom and, optionally, a single oxygen atom..

5. 2-(N-Butyl-N-*iso*butyl)-amino-4-methyloxazole.

6. 4-Methyl-2-(1-piperidino)-oxazole.

7. 2-Di-*iso*propylamino-4,5-dimethyloxazole.

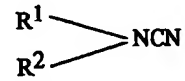
8. 4,5-Dimethyl-2-(N-3-methylbut-1-yn-3-yl-N-propyl)-aminooxazole.

9. 2-(N-Ethyl-N-benzylamino)-4-methyloxazole.

10. 4,5-Dimethyl-2-(4-morpholino)-oxazole.

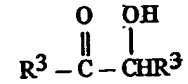
11. A method of preparing of oxazole amine of formula (I) as defined in any one of Claims 1 to 10 which comprises:

(a) reaction of a cyanamide of formula (III):



(III)

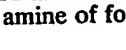
wherein R^1 and R^2 are as defined in any one of Claims 1 to 4, with a hydroxyketone of formula (IV):



(IV)

wherein R^3 and R^4 are as defined in Claim 2:

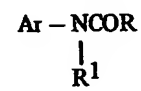
(b) alkylation of a secondary amine of formula (V):



(V)

where Ar is as defined in Claim 1 and R^2 is as defined in any one of Claims 1 to 4;

(c) reduction of the corresponding amide of formula (VI):



(VI)

where Ar is as defined in Claim 1, R^1 is as defined in any one of Claims 1 to 4 and R^5 is R^2 as defined in any one of Claims 1 to 4 less a methylene ($-CH_2-$) group;

(d) reaction of a ketohalo derivative of formula (VII):

$$R^3 - \overset{O}{\overset{\|}{C}} - CHR^4Q \qquad \text{(VII)}$$

where Q is chlorine or bromine and where R^3 is substituted phenyl and R^4 is optionally substituted phenyl, with a substituted urea of formula (VIII):

$$NH_2\overset{O}{\overset{\|}{C}}NR^1R^2 \qquad \text{(VIII)}$$

where R^1 and R^2 are as defined in any one of Claims 1 to 4; or

(e) reaction of a 2-oxazoyl derivative of formula (IX):

ArL (IX)

where Ar is as defined in Claim 1 and L is chlorine, bromine, iodine or a group of formula -SR, SOR, SO_2R where R is C_{1-8} alkyl, C_{3-8} cycloalkyl, benzyl or phenyl at the 2-position of the oxazole nucleus, with an amine of formula HNR^1R^2, where R^1 and R^2 are as defined in any one of Claims 1 to 4.

12. An oxazole amine of formula (I) as defined in Claim 1 substantially as hereinbefore described in any one of Examples 1 to 15.

13. A method of preparing an oxazole amine of formula (I) as defined in Claim 1 substantially as herein before described with reference to any one of Examples 1 to 15.

14. A pharmaceutical formulation comprising an oxazole amine according to any one of Claims 1 to 10 or Claim 12 associated with a pharmaceutically acceptable carrier therefor.

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PRIORITY APPLN. INFO.: GB 1975-24949 A 19760629
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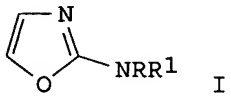

I

AB The oxazole amines I (R, R1 = C1-6 alkyl, C2-6 alkenyl, C3-6 alkynyl, C2-6 alkoxyalkyl, C2-6 carboxyalkyl, C1-6 haloalkyl, C3-10 cycloalkyl, C3-10 cycloalkyl-C1-6 alkyl, optionally substituted Ph, phenylalkyl, or phenylalkenyl; NRR1 = 5-7-membered heterocycle; the oxazole ring is optionally further substituted) were prepared I are useful (no data) in the treatment of immediate hypersensitivity diseases including asthma and in the alleviation of status asthmaticus; they have low toxicity. Thus, 2-(N-butyl-N-isobutyl)amino-4-methyloxazole was prepared from 2-butylamino-4-methyloxazole by treatment in DMF with NaH (0°, 0.5 h) and Me2CHCH2I (room temperature, 11 h).

IT **73801-94-2P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as allergy and asthma inhibitor)
RN 73801-94-2 CAPLUS
CN 2-Oxazolamine, N,N-dibutyl-4,5-bis(4-methoxyphenyl)- (9CI) (CA INDEX NAME)